Anti-platelet treatment is of fundamental importance in combatting functions/dysfunction of platelets in the pathogenesis of cardiovascular and inflammatory diseases. Dysfunction of anucleate platelets is likely to be completely attributable to alterations in protein expression patterns and post-translational modifications. Combining elaborate protocols for platelet isolation from fresh blood donations in conjunction with quantitative mass spectrometry, we created the first comprehensive and quantitative proteome of highly pure human platelets, comprising almost 4,000 unique proteins with copy number estimates for ~3,700 of those and relatively quantified ~1,900 proteins between four different healthy donors - with negligible contamination by leukocytes, erythrocytes and plasma, respectively. For the first time, our data allow for a systematic and weighted appraisal of protein networks and pathways in human platelets, and indicate the feasibility of differential and comprehensive proteome analysis from small blood donations. Since 85% of the platelet proteome show no variation between healthy donors, this study represents the starting point for disease-driven platelet proteomics. These findings allow for correlation to genome-wide association studies which identified in a retrospective manner a set of chromosomal regions affecting the risk of cardiovascular diseases. While respective gene products could be identified in platelets, a comprehensive and quantitative comparison of protein patterns between patients and relevant controls such as relatives and spouses to validate risk factors is still missing. In order to improve cardiovascular risk management, genomic and proteomic analyses of respective corresponding gene loci and proteins using next generation sequencing and targeted MS strategies are applied with the final goal to characterize valuable biomarkers for biomedical screenings.